Subcutaneous interferon alpha 2a combined with cryotherapy vs cryotherapy alone in the treatment of primary anogenital warts: a randomised observer blind placebo controlled study

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Abstract

***Objective*—To compare patient tolerance and treatment efficacy of subcutaneous interferon (IFN) alpha 2a plus cryotherapy versus cryotherapy alone in treatment of primary anogenital (AG) warts.**

***Design*—Randomised placebo controlled observer blind study. Statistical analysis was by chi square and Mann Whitney U tests.**

***Patients*—60 patients with newly diagnosed AG warts.**

***Intervention*—29 and 31 patients were treated with subcutaneous IFN alpha 2a plus cryotherapy or placebo injections plus cryotherapy, respectively.**

***Main outcome measures*—Clinical presence or absence of AG warts. Patients wart-free at 8 weeks were asked to re-attend at 12 weeks; those with persistent warts at 8 weeks were withdrawn from the study.**

***Results*—At 8 weeks 60·7% (17/28 patients) of the IFN group and 67·9% (19/28 patients) of the placebo group were clinically wart-free (not significant); corresponding figures at 12 week review were 29·6% (8/27 patients) and 40% (10/25 patients) respectively (not significant). There was no difference in treatment response between males and females. Recurrence of warts at three month review, in patients cleared of warts at 8 weeks, was seen in 50% (8/16) and 37·5% (6/16) of patients in the IFN and placebo groups respectively (not significant). Multiple warts and the presence of perianal/anal canal warts, either alone or concurrent with warts on the genitalia, at first clinic attendance, were adverse prognostic indicators ($p < 0·001$, and $p = 0·05$ respectively). Cervical human papilloma virus (HPV) infection, exophytic or subclinical, was present in 58·3% and 77·2% of females in the IFN and placebo groups respectively, at trial entry. Although these lesions were not directly treated, colposcopic resolution was seen in 12·5% of affected women, in both treatment groups, by the end of the 7 week treatment period. Systemic side effects were significantly more common in the IFN than in the placebo group, 50% versus 10·7% of patients ($p < 0·01$). Severe influenza like symptoms occurred, after the first three injections only, in one patient treated with IFN; all other reported side effects were mild.**

***Conclusions*—Subcutaneous IFN alpha 2a combined with cryotherapy is no more effective than cryotherapy alone in the treatment of primary AG warts. The presence of multiple warts and perianal/anal canal warts are adverse prognostic indicators.**

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Introduction

Interferon used alone, either topically, intralesionally, or systemically is no more effective than established physical and ablative procedures in the treatment of primary and resistant AG warts.[1–26]

The combination of a physical/chemical ablative procedure with IFN, to treat AG warts is theoretically attractive. The ablative procedure may expose virus particles fragments, and virus infected keratinocytes, to immune and inflammatory cells in the epidermis and upper dermis, stimulating a weak specific/non specific immune response; IFN is an immunostimulant and may augment such a response. In addition IFN may limit local spread of HPV infection by its antiviral and antiproliferative actions.[27]

Thus systemic IFN in combination with a chemical/physical ablative procedure might improve primary clinical cure, and prevent relapse, of AG warts. Few studies using such combination therapy to treat AG warts have been reported; none blind or placebo controlled.[7 22 24 28]

The aims of this study were to compare the clinical response of primary AG warts to systemic IFN in combination with cryotherapy vs cryotherapy alone, to assess patient tolerance to such therapy, and determine if any other factors affect treatment outcome.

Methods

Ethical considerations

Before undertaking the study approval was obtained from the Medical Ethics Committee, Queens University, Belfast.

Recruitment

Patients over the age of 16 years were recruited from genitourinary (GU) clinic attenders with newly diagnosed AG warts, and randomly allocated to IFN or placebo treatment groups. Exclusion criteria were previous treatment for AG warts in the preceding 3 years, past or present immunosuppression for any reason, and pregnancy.

Clinical procedure

Before trial inclusion patients were routinely assessed in the GU clinic, that is clinical examination of the AG tract including proctoscopy, and vaginal speculum in women, rectal, urethral, cervical, and vaginal swabs as appropriate to exclude non specific urethritis (NSU) (diagnosed in males by >10 pus cells on a Gram stained anterior urethral swab and a negative culture for N Gonorrhoeae (GC), non specific genital infection (NSGI) (diagnosed in (1) female sexual partners of males with NSU (2) females with a positive cervical Microtak for *Chlamydia trachomatis*), infections with *N Gonorrhoeae* (GC), *Gardnerella vaginalis* (GV), *Trichomonas vaginalis* (TV), candida, and a blood sample for syphilis serology. In addition females had colposcopy examination, with biopsy of any abnormal representative areas, and pap smear for cervical cytology. Any other infections detected were appropriately treated before trial entry.

According to treatment group allocation, patients were given subcutaneous IFN alpha 2a, in doses of three million units, or placebo (normal saline), on three separate days in the first week. Thereafter patients had IFN, three million units, or placebo injections, twice weekly, and cryotherapy of AG warts once a week, for the following 6 weeks; a total of 7 weeks treatment in all. Cervical warts/subclinical preneoplasias were not specifically treated.

The study was observer blind. Injections of IFN or placebo were administered by a research nurse (HL), and cryotherapy, clinical and colposcopic assessments were performed independently by one observer (JH). At initial assessment and the 8 week review, patients answered a standardised questionnaire, had an AG tract examination including proctoscopy (application of dilute acetic acid to the external AG regions was not performed), cervical pap smear, and colposcopy examination. At the 3 month review patients had repeat AG tract examina-

Table 1 Demographic data of patients with AG warts treated with interferon plus cryotherapy or cryotherapy alone

	IFN/cryotherapy	*Cryotherapy*
Median no. of warts	10	13
Median area of wart tissue (square cm)	2	2
Site of warts (% of patients)		
MALES		
1. inner prepuce/glans/coronal sulcus	40	44·4
2. outer prepuce/penile shaft	20	22·2
3. terminal urethra	14·3	22·2
4. perianal/anal canal	14·3	44·4
FEMALES		
1. introitus	28·6	27·2
2. vulva	71·4	77·2
3. vaginal	0	7·1
4. perianal/anal canal	50	68·2
Morphological wart type (% of patients):		
1. hyperplastic	86·2	77·4
2. sessile	13·7	22·5
3. mixture of 1/2	6·9	9·6
Male sexual behaviour (no. of patients):		
1. heterosexual	14	9
2. homosexual	1	0
TOTAL	15	9
Female sexual behaviour (no. of patients):		
1. heterosexual	13	22
2. virgin	1	0
TOTAL	14	22
Total no. of patients	29	31

Table 2 Prevalence of AG warts at eight week review in patients treated with IFN plus cryotherapy and cryotherapy alone

	No. of patients	
	IFN/ cryotherapy	*Placebo/ cryotherapy*
Clinical cure	17 (60·7%)	19 (67·9%)
Persistent warts	11	9
Dropouts	1	3
Total (excluding dropouts)	28 (100%)	28 (100%)

Table 3 Prevalence of AG warts at three month review in patients treated with IFN plus cryotherapy and cryotherapy alone

	No. of patients	
	IFN/ cryotherapy	*Placebo/ cryotherapy*
Clinical cure	8 (29·6%)	10 (40%)
Persistent warts	19 (70·4%)	15 (60%)
a. withdrawn at 8 weeks	11	9
b. recurrence after cure at 8 weeks	8	6
Dropouts	2	6
Total (excluding dropouts)	27 (100%)	25 (100%)

tion with proctoscopy. All biopsy and cytology specimens were analysed in routine cytology and histopathology laboratories.

Cryotherapy was performed with a standard cryoprobe, after prior application of KY jelly to the wart(s), for a single 60 second freeze. When required local anaesthetic cream (EMLA) was applied instead of KY gel. Patients were instructed to bathe in saline twice daily, until healing of treated areas was complete.

At 8 week review patients clinically clear of AG warts were asked to re attend a further four to six weeks later; those who had persistent warts at 8 weeks were withdrawn from the study. During the study period patients were advised either to avoid sexual intercourse, or to use condoms during intercourse.

Results

Demographic data

Twenty nine patients were included in the IFN group, and 31 in the placebo group. There were no significant demographic differences between patients in the two treatment groups (table 1).

Treatment efficacy

Four patients, one in the IFN and three in the placebo group, failed to complete the 7 week treatment course. Three were withdrawn because they missed two treatment sessions; one was withdrawn because of pregnancy. No patient dropped out or was withdrawn because of side effects.

Table 2 shows results at eight week review. There was no significant difference in overall clinical response between the two treatment groups, or between males and females within each treatment group.

Of 17 and 19 patients clinically clear of warts at 8 weeks in the IFN and placebo treatment groups respectively, 16 in both groups reattended for 3 month review. Recurrence of warts was seen in 50% (8/16) of patients in the IFN group, and 37·5% (6/16) patients in the placebo group. There was no significant difference in clinical response at three month review between the treatment groups (table 3). These figures were calculated assuming patients withdrawn with persistent warts at 8 weeks, would still have had their warts at 3 months without further treatment in the intervening period.

Resolution of cervical lesions was seen in 1/8 patients in the IFN group, and 2/16 patients in the placebo group.

Tables 4 and 5 summarise the importance of other factors in determining treatment outcome. The presence of multiple warts (Mann Whitney U $p < 0·001$), and perianal/anal canal warts (chi square

Table 4 Factors determining outcome at 8 week review in patients with primary AG warts treated with IFN plus cryotherapy and cryotherapy alone

	No. of patients cured of warts at 8 week review		*Significance (p) (Chi square)*
1. Sex	male	17/23	NS
	female	19/33	
2. Other AG tract infection at 1st visit	present	19/32	NS
	none	17/24	
3. Site of warts	genital only	24/30	0·05
	gen + perianal/perianal only	12/26	
4. Cervical warts virus infection at 1st visit	present	13/22	NS
	none	4/9	
5. Protected Int. during treatment	yes	20/35	NS
	no int.	16/21	
6. Unprotected int. during treatment	yes	3/5	NS
	none	33/51	

Table 5 Importance of number, area, and duration of AG warts in determination of outcome at 8 eight week review in patients treated with IFN plus cryotherapy and cryotherapy alone

	Patients		
	free of warts	*persistent warts*	*p values*
No. warts at first visit (median/range)	7/1–25	16/6–26	<0·001
Area of wart tissue (square cm) (median/range)	1/1–3	1/1–3	NS
Wart duration prior to first visit (months, median/range)	2/0–36	2/0–36	NS
No. of patients	36	20	

p = 0·05), at trial entry, were associated with significantly worse prognosis.

Side effects

Side effects of cryotherapy were local irritation, blistering, and ulceration. These were generally well tolerated and resolved within 7 to 10 days. No secondary infection necessitating treatment occurred.

Systemic side effects were reported significantly more frequently in the IFN/cryotherapy group (chi squared p < 0·01). (table 6). In the IFN/cryo group fever like symptoms occurred within 24 hours following injection, usually only after the first two to three injections. Headache and fatigue were reported both directly after injection and continuously, apparently unrelated to injections. With the exception of one male patient who experienced severe fever, myalgia and nausea which necessitated bed rest for 48 hours after the first IFN injection, all other reported side effects were mild. No patient stopped therapy or was withdrawn from the study because of side effects.

Discussion

Although this study was of a small number of patients with relatively short post treatment follow up, the results provide no evidence to suggest systemic IFN combined with cryotherapy is more effective than cryotherapy alone in the treatment of AG warts. Three month figures reported in this study based on the assumption no warts present on completion of treatment are likely to regress in the following four to six weeks, either spontaneously or through residual effects of treatment, may slightly underestimate true clinical response at this time.

Table 6 Systemic side effects reported during study period in patients with AG warts treated with IFN plus cryotherapy and cryotherapy alone

	No. of patients	
	IFN/ cryotherapy	*Placebo/ cryotherapy*
Fever post injection	8	2
Headache	3	1
Fatigue	1	1
Myalgia	2	0
Foul taste in mouth	1	0
Stomach cramps	1	0
Mood disturbance	0	1
Total no. patients with systemic side effects	14	3*
Total no. patients completing treatment	28	28

*chi square p < 0·01.

A possible explanation for our findings is lack of exposure of HPV infected keratinocytes within warts to concentrations of IFN high enough to (1) stimulate an effective specfic immune response against either intracellular HPV or viral related antigen expressed on the surface of infected cells (2) prevent intracellular viral replication and transcription.

The relative lack of side effects seen in IFN treated patients in this study, should enable a similar study using higher doses of IFN to be undertaken. However, evidence from studies treating AG warts with IFN alone, suggests increasing doses of IFN, to a maximum limited by side effects, does not significantly improve treatment efficacy.[19 20 29]

Few studies using IFN in combination with other modalities are reported. Only a minority of these studies directly compare combinaton therapy with the relevant single established treatment; none of these studies are placebo controlled.[7 22 24 28]

One study reported clinical cure of 51% of warts treated with intralesional IFN and cryotherapy vs 15% of warts treated by cryotherapy alone.[7]

Other comparative studies report 90% cure of warts treated with IFN plus electrocoagulation vs 80% cure of warts treated with electrocoagulation alone.[24] Intralesional IFN plus podophyllin gave rates of 67% cure of treated warts vs 43% cure of warts treated with podophyllin alone,[7] and a study comparing patients with warts treated with subcutaneous IFN plus podophyllin, podophyllin alone, and IFN alone, reported clinical cure in 31%, 11%, and 28% of patients respectively.[22] Bichloracetic acid (BCA) plus IFN was superior to BCA alone in treatment of AG warts.[28]

Cure rates of 95% in patients with warts treated by intralesional IFN followed by laser ablation, and

87·5% in patients treated with intramuscular IFN plus laser ablation are reported.[28]

All these studies must be interpreted in light of reported efficacy of single agent therapy of AG warts; laser ablation 65–97% clinical cure after a single treatment,[30-37] electrocautery/coagulation 71–90% clinical cure after a single treatment,[24 38-42] cryotherapy 55–100% cure after repeated treatments,[43-47] podophyllin 22–76% cure after treatment courses.[39 48-54]

It has been suggested IFN combination therapy may lower the recurrence rate in patients clinically cleared of warts by chemical/surgical modalities. Recurrence after most surgical procedures is estimated around 10–15%, and between 0–69% for podophyllin treated lesions.[39 49 50 52-54] Our results do not support this assumption.

In conclusion our findings suggest IFN plus cryotherapy is no more effective than cryotherapy alone in treatment of primary AG warts; adverse clinical prognostic factors are multiple warts and presence of warts in the perianal/anal canal regions.

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